

REMARKS

Claims 1-74 have been canceled, and 75-147 are pending for the Examiner's consideration. Claims 75, 77, 78, 80, 81, and 85-95 are amended herein. New claims 96-147 have been added. Applicant respectfully submits that these amendments introduce no new matter. Support for the new claims can be found in the specification and original claims. Applicant respectfully requests entry of the present amendment in view of the Request for Continued Examination ("RCE") filed herewith.

Applicants' attorneys would like to thank Examiner Dentz for kindly granting an interview on September 29, 2005.

I. Claim Amendments and Support

Applicants submit that the amended and new claims are supported in the specification and claims and support for selected language is as follows: Claims 75 and 85 to an isolated mixture of theaflavin is supported by Example 1 on pages 19-20, the bridging paragraph on pages 4-5; and the bridging paragraph on pages 9-10, Claims containing the term "pharmaceutically acceptable vehicle" and types of vehicles is supported on page 6, 1st complete paragraph; Claims containing forms of pharmaceutical compositions, such as capsules, stabilizers, agents, oils are supported beginning on page 15, and in the middle of page 16 under the heading, Pharmaceutical Compositions; Claims containing range of %s for the 4 theaflavins are supported on page 10 , 2nd complete paragraph and on page 15, last paragraph; and Claims directed to soft gels with oil are supported by Example 3.

II. Rejection Under 35 U.S.C. § 102(b)

Claims 75-95 were rejected under 35 U.S.C. § 102(b) as anticipated by Vitasyn, DE 19627344 A1 (translation) for the same reasons that previous claims 15, 16, 28, 29, 34, 35, 38, 58 and 59 were anticipated in the previous office action. The Examiner alleges that Vitasyn

discloses the benefits of the polyphenol constituents of both green tea and its fermented form, which is black tea, for the treatment of hyperlipidemia. The Examiner further cites page 2 of the translation and claims 1, 14 and 18 to support his rejection. Applicants respectfully traverse this rejection and wish to point out that the claims are directed to a method of reducing LDLs while not significantly reducing HDLs comprising administering **an isolated mixture** of theaflavin, theaflavin-3-gallate, theaflavin-3'-gallate, and theaflavin 3,3'-digallate or a **composition consisting essentially of a mixture** of theaflavin, theaflavin-3-gallate, theaflavin-3'-gallate, and theaflavin 3,3'-digallate or another recited amount or formulation of the 4 recited theaflavins in a therapeutically effective amount and for a time period sufficient to reduce the LDL while not significantly reducing the HDL over the time of administration, and a daily dosage composition for oral administration, which comprises such mixtures and compositions of the 4 recited theaflavins. in a therapeutically effective amount and for a time period sufficient to reduce the LDL while not significantly reducing the HDL over the time of administration.

The Examiner refers to claim 1 of Vitasyn as disclosing a pharmaceutical composition containing theaflavins and claims 14 and 18 for its use in treating hypercholesterolemia and lipid metabolism, respectively. However, all that Vitasyn's preparation discloses is a laundry list of substances. Vitasyn does not disclose a method of treating hyperlipidemia with a composition that contains specific mixtures of theaflavin, theaflavin-3-gallate, theaflavin-3'-gallate, and theaflavin 3,3'-digallate resulting in the recited outcome that reduces LDLs while not significantly reducing HDLs. Applicants have added additional independent and dependent claims to encompass theaflavin mixtures useful in the present invention. These additional claims cover compositions containing the theaflavins at specific percentage ranges or dosage amounts.

Applicants submit that the amended claims that are presently pending are not anticipated by Vitasyn and it is requested that this rejection be withdrawn.

III. Rejection Under 35 U.S.C. § 103

Claims 75-95 were rejected under 35 U.S.C. § 103 as obvious over Vitasyn, DE 19627344 A1 (translation) for the same reasons that previous claims 15, 16, 28, 29, 34, 35, 38, 58 and 59 were considered to be obvious in the previous office action. The Examiner alleges that it would be obvious to treat hypercholesterolemia and the other enumerated diseases with the enumerated theaflavin ingredients. For the same reasons that the pending claims were not anticipated by Vitasyn's preparation as argued above, it is not obvious to treat a human to reduce the LDLs but have no significant reduction in the HDLs using the claimed mixtures of theaflavins. The claims disclose specific theaflavin compositions that are not suggested by Vitasyn's preparation nor does Vitasyn suggest such treatment could be expected to result in reduction in LDLs and no significant reduction in HDLs as claimed by applications. For the foregoing reasons, it is requested that this rejection be withdrawn as to the pending claims.

IV. Rejection Under 35 U.S.C. § 102(b)

Claims 75-95 were rejected under 35 U.S.C. § 102(b) as anticipated by Abe *et al.* ("Abe") for the same reasons that previous claims 15, 16, 28, 29, 34, 35, 38, 58 and 59 were anticipated in the previous office action. The Examiner alleges that Abe discloses that theaflavins in black tea are excellent inhibitors of squalene epoxidase, the rate-limiting enzyme of cholesterol biosynthesis, and concludes that the method of treating hyperlipidemia by administering to a patient a theaflavin mixture is anticipated. Applicants respectfully traverse this rejection and would like to point out that Abe discloses an *in vitro* assay to show that in the presence of

theaflavin, squalene monooxygenase activity is inhibited, the inhibition concentration is 1 μ M to 5 μ M (600 μ g to 3,000 μ g)/liter. Abe simply does not disclose applicants' claimed method of treatment or applicants' dosage form. Therefore, Able does not anticipate the presently pending claims to a method of reducing LDL in a human subject and a daily dosage form to treat the subject. It is requested that this rejection be withdrawn.

V. Rejection Under 35 U.S.C. § 103)

Claims 75-95 were rejected under 35 U.S.C. § 103 as obvious over Abe *et al.* ("Abe") for the same reasons that previous claims 15, 16, 28, 29, 34, 35, 38, 58 and 59 were considered to be obvious in the previous office action. The Examiner alleges that Abe discloses that black tea would be expected to be an excellent beverage to lower cholesterol, and thus using theaflavins as presently claimed would be obvious. Again Abe does not disclose treating humans or disclose the claimed daily dosage for treatment. As squalene monooxygenase is one of many enzymes involved in cholesterol biosynthesis, it is our position that Abe's results are not predictive of the effect of theaflavin on the inhibition of cholesterol biogenesis *in vivo* with the same mechanism, and there has been continuing research to support this unpredictability *in vivo*.

First of all, experiments conducted *in vivo* determined that theaflavins do not go into the body as theaflavins. Theaflavins go through biotransformation in the digestion system (See Exhibit A, Jhoo *et al.*, 2005). This study shows that when theaflavin goes through the digestion system, it becomes a molecule called theanaphthoquinone. The Jhoo study shows that very low levels of theaflavins can be detected in the serum. Therefore, it is unlikely that the squalene monooxygenase that is found in liver cells will not come in contact with theaflavins molecules. Therefore, the Jhoo study suggests that Abe's results will be difficult to repeat *in vivo*, and thus

renders the outcome unpredictable. In further support of this position, another study shows that after administration of theaflavin, only minute amounts of theaflavin can be detected in serum (See Exhibit B - Mulder *et al*, 2001, page 271, the last sentence in the abstract; page 278, first paragraph -). Again with such minute levels of theaflavin, it is not likely that theaflavin in the body would come in contact with squalene monooxygenase to inhibit this enzyme and cause a reduction in cholesterol synthesis *in vivo*.

An additional point supporting unpredictability is that it is known that theaflavin is very unstable and degrades into other forms in the digestion system (See Exhibit C - Su *et al*, 2003, page 192, where the pH in intestine is basic and theaflavin will be degraded into metabolites very quickly).

Applicants submit that one cannot use the results from *in vitro* studies to simply predict the results *in vivo*, particularly with the Abe study which analyzed the inhibition of squalene monooxygenase in a test tube. Without more evidence of use in an animal or human or higher *in vivo* levels or stability, applicants submit that the results in Abe are not predictive of the outcome in human subjects.

The present invention discloses the unique lipid profile of animals and humans as the result of the administration of theaflavins. Applicants have shown that the oral administration of theaflavins results in a different effect on each lipid component. Applicants' results demonstrate that there is no change of HDL cholesterol and triglycerol levels. However, total cholesterol level is lowered about 11%, and LDL level is lowered by 17%. LDL is the risk factor that is most closely linked to cardiovascular diseases. So the finding has clinical significance.

In summary, the effect of theaflavin on the cholesterol panel is very complicated. Research supported by Exhibits A-C, and submitted herewith, has shown that theaflavin has very

low bioavailability in animals, is present in minute quantities in serum and has a very low likelihood of coming into contact with squalene monooxygenase *in vivo*. Therefore, Abe does not provide a motivation or suggest to a person skilled in the art that theaflavin would be useful for lowering LDL while not significantly reducing HDL. In view of these arguments, it is requested that this rejection be withdrawn to the presently pending claims.

Conclusion

All of the stated grounds of rejection have been properly traversed or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all presently outstanding rejections. Applicants believe that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment is respectfully requested.

Respectfully submitted,
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